AMENDMENT

In the claims:

Please amend the claims as follows:

1 (Previously Amended). A genetically engineered mammalian cell that has been mutated by a process comprising the insertion of a recombinantly manipulated polynucleotide sequence into a gene in said genetically engineered mammalian cell wherein said gene is identifiable as corresponding to SEQ ID NO:2.

2 (Original). The genetically engineered mammalian cell of Claim 1, wherein said cell is murine.

3 (Previously Amended). A cell according to Claim 2, wherein said cell is a mouse embryonic stem cell.

4 (Original). The genetically engineered mammalian cell of Claim 1, wherein said polynucleotide sequence is present on a viral vector.

5 (Original). A cell according to Claim 4, wherein said viral vector is a retroviral vector.

6 (Original). A cell according to Claim 4, wherein said viral vector additionally comprises regions of targeting DNA that facilitate gene targeting by homologous recombination.

7 (Previously Amended). An isolated mouse embryonic stem cell line comprising an engineered retroviral gene trap vector in at least one gene comprising a polynucleotide sequence identifiable as corresponding to SEQ ID NO:2 .

RESPONSE

SUMMARY OF THE INVENTION

The present claims are directed to novel cell lines comprising an genetically engineered mutation in the mouse ortholog of a human gene. Like most patented cell lines, the described cells are useful as tumor models, for the expression of genetically engineered products, and for the identification and characterization of biochemical pathways. *Unlike* most patented cell lines, the described cells are totipotent embryonic stem cells. As totipotent cells, embryonic stem cells have a normal compliment of chromosomes (unlike most patented aneuploid cell lines) and can thus be introduced into an embryo (by microinjection , morula aggregation, etc.) and used to give rise to animals that are essentially wholly genetically derived from the ES cell. When, as in the present case, the ES cell clone has been manipulated *in vitro* to contain a genetically engineered allele, the ES cell clone can be used to generate live animals capable of germ line transmission of the genetically engineered allele. These animals can then be used to determine the physiological function of the mutated gene through standard genetic analysis (which discerns the normal function of a gene via which physiological systems are perturbed by the engineered alteration of gene function). In the present instance, when a certain embodiment of the claimed mutated mammalian cells (*i.e.*, an ES line embodiment) was used to produce animals homozygous for the mutation in the mouse gene that naturally encodes the exon sequence described in SEQ ID NO:2, the animals produced as taught in the specification displayed marked hyperactivity. In brief, the specifically described ES cell line was used to determine that the gene mutated in the described ES cell line may present a novel means of drug intervention for the treatment or prevention of, *inter alia*, attention deficit hyperactivity disorder (*i.e.*, a drug that antagonizes the targeted protein, should impact the same physiological pathway contributing to the observed hyperactivity since the described animals have been genetically manipulated to presage the action of the "perfect" drug– a drug that specifically targets and ablates the function of the targeted protein– bearing in mind that, in pre-adolescent humans, the observed behavioral effect is often in the opposite direction of drug action in adults, *e.g.*, ritalin). Given the clear medical importance of behavioral disorders in western medicine (not to mention classrooms), it is clear that the above discovery clearly defines a patentable and useful invention.

In summary, a review of patents issued over the last several decades indicates that non-totipotent cell lines constitute patentable subject matter (5,985,290, 5,288,628, etc.), ES cell lines constitute patentable subject matter (U.S. Patent No. 6,200,806), vectors and methods of genetically manipulating

ES cell lines constitute patentable subject matter (U.S. Patents Nos. 6,207,371, 6,204,061, 5,789,215, etc.), and that genetically engineered mice constitute patentable subject matter (5,948,952, 4,736,866, etc.)– and especially, as in the present case, genetically engineered mice that define a novel modes of medical intervention. Thus, the only remaining question for the present inquiry is where and how in the above continuum of patentable scientific utility, the utility of the described ES cell line has somehow vanished?

RESPONSE

I. Status of the Claims

Claims 1-7 are presently pending and presently stand as rejected under 35 USC §§101/112. No prior art rejections are presently of record.

II. The Present Claims Are Patentable And The Rejections of Record Should Be Withdrawn.

a) Rejections Under 35 U.S.C. § 101 and §112, First Paragraph

The Examiner's rejections of Claims 1-7 under 35 U.S.C. section 101 and the intertwined rejections under section 112, first paragraph are respectfully traversed. The Examiner has apparently adopted the position that the claimed invention lacks patentable utility due to its not being supported by either a specific and/or substantial utility or a well established utility. The Examiner's position seems to be predicated on three basic assumptions: 1) The mutated gene wasn't known at the time the invention was filed (at page 3 of the Action); 2) The specification does not contemplate mice derived from the described ES cells (at page 4 of the Action); and 3) The application did not presage the phenotype. Two of the above assumptions are clearly erroneous (as dealt with below), and the third assumption basically provides the fundamental motivation for the broader application since no bioinformatics, biochemical, or *in vitro* cell-based systems (many of which have been patented) have proven capable of reliably presaging the physiological function of gene products.

When cells exemplary of the described ES cell line were used to generate mice homozygous for the mutation that was genetically engineered into the gene at issue (see GENSEQ accession no. Y84372 as identified in Figure 2, line 2 of the instant application– A courtesy copy of the GENSEQ annotation for this accession no. is being provided herewith as Exhibit A which shows that scientists had identified the mutated gene as encoding a voltage-gated calcium channel as early as 1998), the mice exhibited

marked hyperactivity. Exhibit A provides dispositive evidence of record that the identity of the CACNG8 gene was indeed known at the time the present application was filed.

The use of the described ES cells (using well-established methods that are widely known in the art, see, for example, U.S. Patent No. 6,207,371 at columns 15-16 which was incorporated by reference into the present specification) to produce animals that stably maintain the mutated allele are specifically contemplated in the last paragraph of the Summary of the Invention (pages 3-4). In view of the clear phenotype/medical discovery attributable to the described ES cells, little question can remain that the described ES cell lines have a substantial and specific "real world" utility. In summary, when the described ES cells were used to produced mutant animals *as specifically contemplated in the specification*, the resulting animals had a profound and medically relevant behavioral phenotype. Given that here can be no question that the described genetically engineered animals define a patentable utility, how not the engineered ES cells used to generate the animals? From a practical stand point, the present quandary presents a mammalian version of the age old chicken-or-the-egg paradox. In this case, it is clear that a patentable genetically engineered chicken would produce patentable eggs which would then produce patentable chickens....

Finally, the Examiner has seemed to imply that the present invention cannot have utility because the functional properties of the mutated gene were not previously known. This naturally begs the question, if the physiological function of a given sequence was actually already known, why do the experiment? One point worth raising here is that although the commercial utility of doing such a hypothetical experiment might be questionable, there would be little question that, according to the Examiner's logic, the experiment would almost certainly have a patentable utility (which is somewhat illustrative of the crosswise logic/policy considerations presently guiding the broader utility debate within the field). Again, the systemic failure within the larger scientific community to reliably predict physiological function from bioinformatics, expression data, proteomics, biochemical activity, and cell-based data has largely motivated the present scientific inquiry and invention. Once the erroneous policy and administrative considerations are stripped-away, the scientific and commercial considerations that will necessarily drive the development of new pharmaceutical products can logically control the relevant practical analysis. It is this practical analysis that the utility provisions of the patent code are meant to address.

From a purely practical perspective, Applicants respectfully request that the Examiner consider a commercial "nuts-and-bolts practical/industrial" utility for the described ES cell clones. In addition

to their generation and study, the storage, handling, and transfer of genetically engineered mice is a rather expensive commercial endeavor. Unlike most academic facilities, industrial vivariums are typically run under pathogen-free "barrier" conditions and extensive efforts are undertaken to protect the pathogen free status of the various animal colonies. Consequently, new colonies being brought into the barrier are often "rederived" (often using ES cells) into the barrier via birth from "clean" surrogate mothers animals. That's one practical use of the described ES cell clones.

Additionally, space in such facilities is often at a substantial premium. Unlike live animals, mutated ES cell clones can be stored in liquid nitrogen. Tens of thousands of mutated ES cell clones can be stored in a couple of liquid nitrogen freezers whereas many hundreds of thousands of square feet of "barrier" vivarium space would be necessary to store corresponding numbers of live mutant animal colonies. From a practical storage perspective, a couple of microtiter plates can roughly correspond to an entire room of vivarium space (the absence of such practical efficiencies largely contributed to the broader failure of the NIH's efforts to approach attack gene function through ENU mutagenesis in live mouse colonies). In brief, although the biotech utility analysis has typically focused on scientific nuances bordering on the metaphysical, the practical savings and efficiencies of working with ES cell clones provide an industrial utility that is not dissimilar from the efficiencies obtained between storing paper files as compared to digital data storage– an industrial utility clearly recognized by the U.S. Patent Office as evidenced by its recent adoption of electronic document storage. Accordingly, there can be no question of the industrial utility of the more broadly described invention.

In view of the overwhelming evidence of the substantial, credible, specific, and well-established utility of the presently claimed invention, and in view of the absence of any evidence of record specifically refuting the utility of the described ES cell clones, the Applicants' respectfully request that the Examiner withdraw the pending rejection of Claim 8 under 35 U.S.C. section 101 as well as the related rejections under 35 U.S.C. section 112, first paragraph.

b) Additional Rejections under 35 U.S.C. Section 112, First Paragraph

The Examiner has also rejected Claims 1-7 under 35 U.S.C. section 112, first paragraph for allegedly failing to comply with the written description requirement. As discussed in a prior response, those skilled in the art would understand that in order to generate the sequence tags described in the specification and Sequence Listing, the Applicants must necessarily be in possession of the described ES cell clones. Thus, there can be no scientifically credible assertion that the Applicants were not IN